Chloroquine

Chloroquine is a 4-aminoquinoline compound that has been used extensively for the treatment and prevention of malaria.

From: Nanoarchitectonics for Smart Delivery and Drug Targeting, 2016

Related terms:

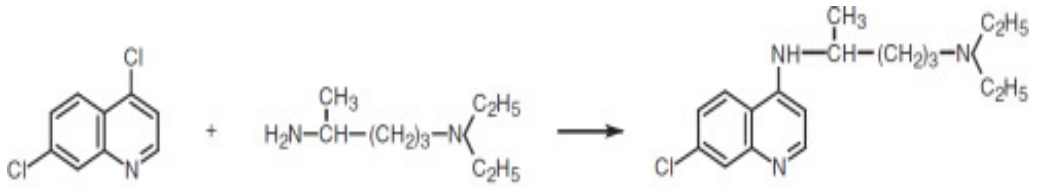
Antimalarial Activity, Mefloquine, Protein, Quinine, Alkaloid, Quinoline, Antimalarial, Antiplasmodic, Antimalarial Agent

Drugs for Treating Protozoan Infections

R.S. Vardanyan, V.J. Hruby, in Synthesis of Essential Drugs, 2006

Chloroquine

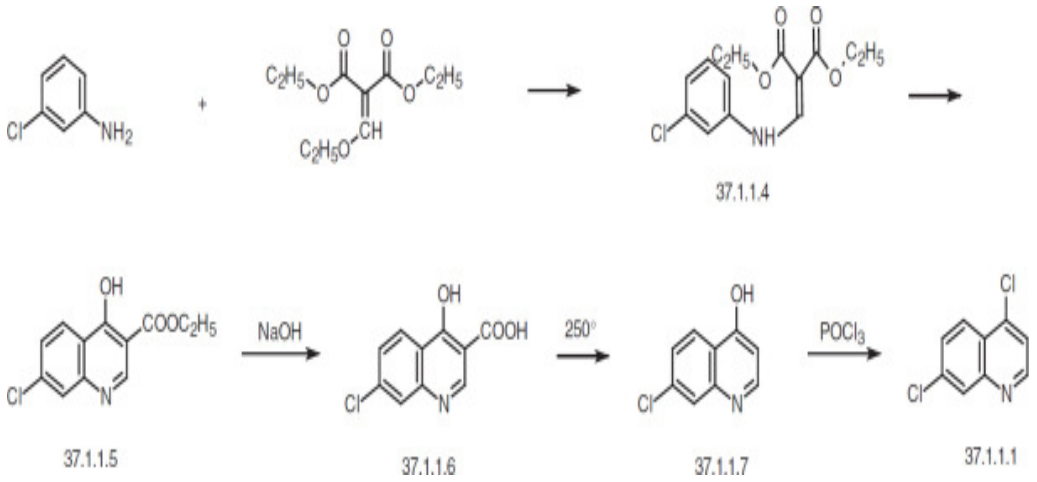
Chloroquine, 7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline (37.1.3), is made by reacting 4,7-dichloroquinoline (37.1.1.1) with 4-diethylamino-1-methylbutylamine (37.1.1.2) at 180 °C [1–3].



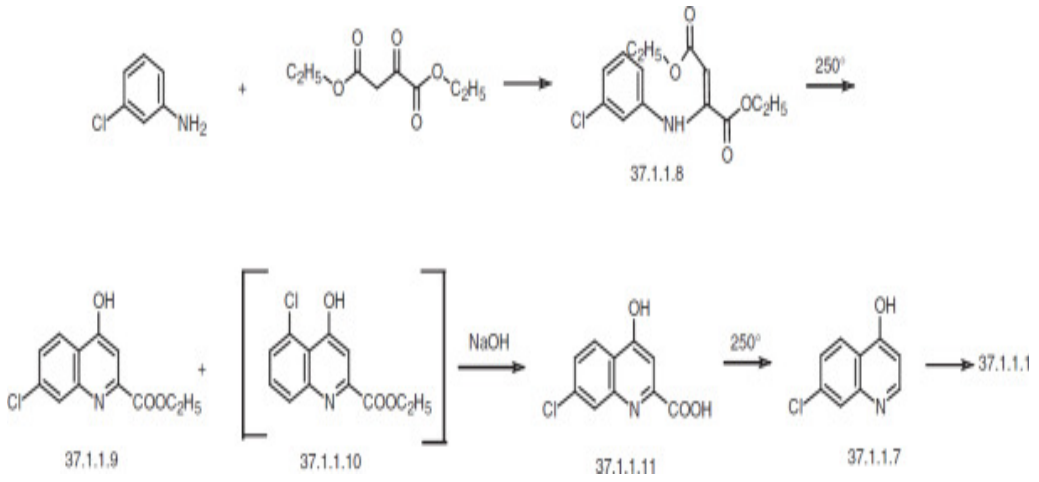
37.1.1.1 37.1.1.2 37.1.1.3

In order to realize the synthesis, the necessary 4,7-dichloroquinoline (37.1.1.1) is prepared in several ways from 3-chloroaniline. One of these ways consists of reacting 3-chloroaniline with ethoxymethylenmalonic ester to make (3-choroanilino)-methylenemalonic ester (37.1.1.4), which then undergoes high-temperature heterocyclization to make the ethyl ester of 7-chloro-4-hydroxyquinolin-3-carboxylic acid (37.1.1.5). Hydrolyzing this with

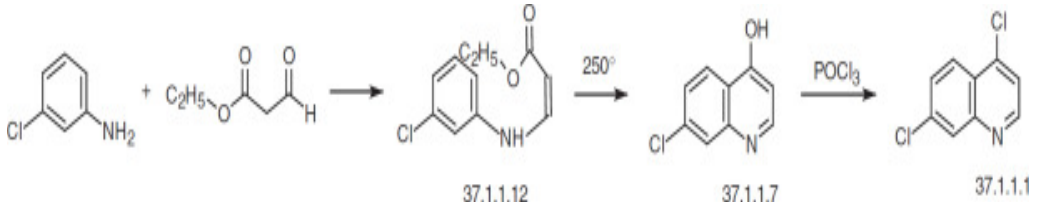
sodium hydroxide gives 7-chloro-4-hydroxyquinolin-3-decarboxylic acid (37.1.1.6), which when heated at 250–270 C is decarboxylated, forming 7-chloro-4-hydroxyquinoline (37.1.1.7). Treating this with phosphorus oxychloride gives one of the desired components for synthesis of chloroquine – 4,7-dichloroquinoline (37.1.1.1) [4,5].



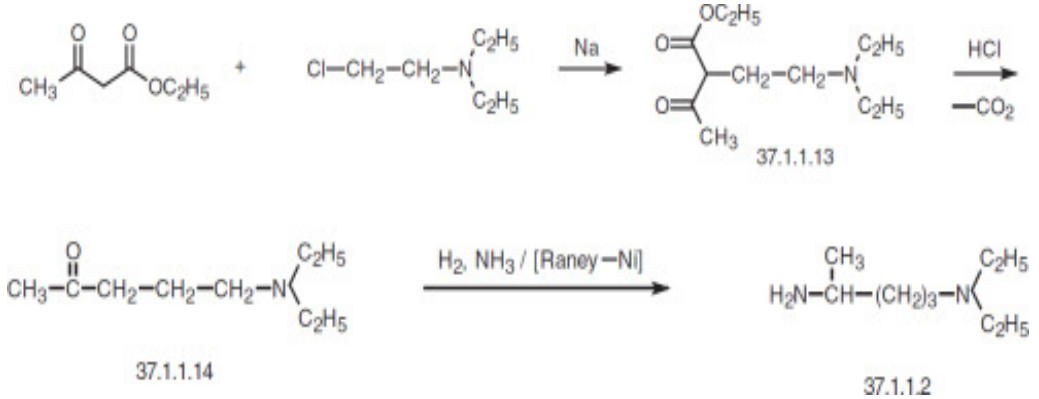
The second method of preparing of 4,7-dichloroquinoline (37.1.1.1) consists of reacting 3-chloroaniline with the diethyl ester of oxaloacetic acid in the presence of acetic acid to give the corresponding enamine (37.1.1.8), which when heated to 250 °C undergoes heterocyclization to the ethyl ester of 7-chloro-4-hydrozyquinolin-2-carboxylic acid (37.1.1.9) accompanied with a small amount of 5-chloro-4-hydroxyquinolin-2-carboxylic acid (37.1.1.10), which is separated from the main product by crystallization from acetic acid. Alkaline hydrolysis of the ethyl ester of the 7-chloro-4-hydroxyquinolin-2-carboxylic acid (37.1.1.9) and subsequent high-temperature decarboxylation of the resulting acid (37.1.1.11) gives 7-chloro-4-hydroxyquinolin (37.1.1.7). Reacting this with phosphorus oxychloride using the scheme described above gives 4,7-dichloroquineoline (37.1.1.1) [6].



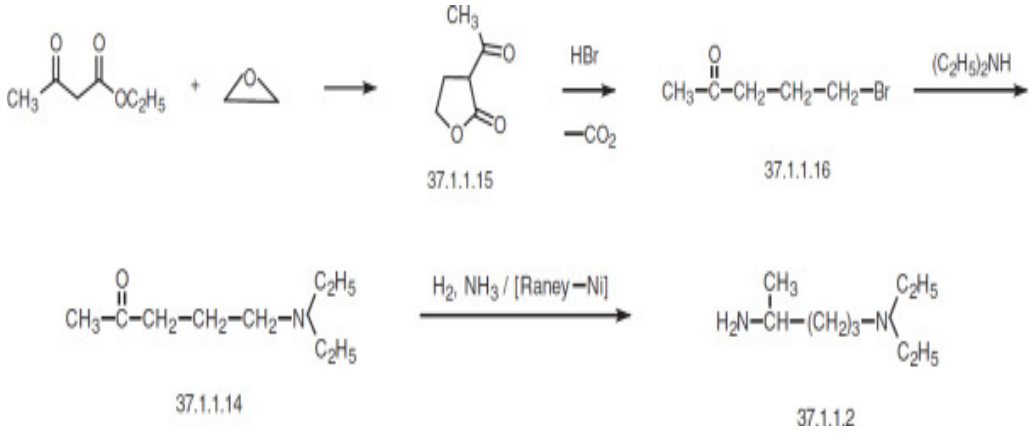
Finally, the third of the suggested variants for making 4,7-dichloroquinoline (37.1.1.1) consists of reacting 3-chloroaniline with the ethyl ester of formylacetic acid to make the enamine (37.1.1.12), which on heating directly cyclizes to 7-chloro-4-hydroxyquinoline (37.1.1.7). Reacting this with phophorus oxychloride according to the scheme already described gives 4,7-dichloroquinoline (37.1.1.1) [7].



The second component necessary for synthesizing of the chloroquine is 4-diethylamino-1-methylbutylamine (37.1.1.2), is also made in various ways. Alkylating acetoacetic ester with 2-diethylaminoethylchloride gives 2-diethylaminoethylacetoacetic acid ester (37.1.1.13), which upon acidic hydrolysis (using hydrochloric acid) and simultaneous decarboxylation makes 1-diethylamino-4-pentanone (37.1.1.14). Reductive amination of this compound with hydrogen and ammonia using Raney nickel as a catalyst gives 4-diethylamino-1-methylbutylamine (37.1.1.2) [8].



Another way suggested for making 4-diethylamino-1-methylbutylamine (37.1.1.2) is by starting with 3-acetylbutyrolactone (37.1.1.15), which is made by reacting acetoacetic acid ester with ethylenoxide. Acidic hydrolysis of the ester group in 3-acetylbutyrolactone (37.1.1.15) along with simultaneous decarboxylation gives 1-bromo-4-pentanone (37.1.1.16). Reacting this with diethylamine gives 1-diethylamino-4-pentanone (37.1.1.14), and reductive amination of this compound using hydrogen and ammonia using Raney nickel as a catalyst gives 4-diethyl-1-methylbutylamine (37.1.1.2) [9].



37.1.1.15 37.1.1.16 37.1.1.14 37.1.1.2

Chloroquine is the drug of choice for preventing and treating acute forms of malaria caused by *P. vivax, P. malariae, P. ovale*, as well as sensitive forms of *P. falciparum*. The mechanism of its action is not completely clear, although there are several hypotheses explaining its antimalarial activity. Chloroquine and its analogs inhibit synthesis of nucleic acids of the parasite by affecting the matrix function of DNA. This happens by preliminary binding of the drug through hydrogen bonds with the purine fragments, and subsequent introduction of the chloroquine molecule between the orderly arranged base pairs into the spirals of the DNA of the parasite. Thus chloroquine prevents transcription and translation, which significantly limits the synthesis of DNA and RNA in the parasite. The selective toxicity of chloroquine in particular with respect to malarial plasmodia is also attributed to the ability of the parasitized red blood cells to concentrate the drug in amounts approximately 25 times greater than in normal erythrocytes. There is also a different hypothesis. Chloroquine has a high affinity for tissues of the parasite and is concentrated in its cytoplasm. As a weak base, it increases the pH of the intracellular lysosome and endosome. A more acidic medium in these organelles is needed for the parasite to affect mammalian cells. As a result, chloroquine inhibits growth and development of parasites.

Thus the main quality of chloroquine that exceeds all other antimalarial drug

is its effect on erythrocytic schizonts (hematoschizotropic action). However, chloroquine also possesses amebicidal action. It has also been observed to have immunodepressive and antiarrhythmic properties.

It is used for all types of malaria, for chemotherapy, as well as for non-gastric amebiasis, and amebic abscesses of the liver. Synonyms of this drug are nivaquine, quingamine, delagil, resoquine, atroquine, and others.

Therapeutic Areas II: Cancer, Infectious Diseases, Inflammation & Immunology and Dermatology

K.M. Muraleedharan, M.A. Avery, in Comprehensive Medicinal Chemistry II, 2007

7.27.5.1.1.1 4-Aminoquinolines

Chloroquine (CQ, **2**) was developed as a result of intense antimalarial drug development efforts in the USA during World War II, but the compound was familiar to Germans as early as 1934 under the name resochin.[176] The safety, efficacy, and low cost brought chloroquine to the front lines to treat malaria, and it was used extensively for almost two decades after its first introduction in 1944–45 – until the parasites developed resistance in the 1960s. Amodiaquine (AQ, **3**) is structurally related to CQ and is active against drug-resistant strains of *P. falciparum*.[180,181] Even though it is more effective in parasite clearance than CQ, the clinical use of amodiaquine has been limited due to hepatotoxicity, agranulocytosis, and cross-resistance with CQ.[182] Pyronaridine (**4**), an acridine derivative having resemblance to CQ and AQ, was first developed in China in 1970 and has proven to be very effective against all four *Plasmodium* species affecting humans, including drug-resistant strains.[183–185]

Members of the quinoline family in general exert their effect during the intraerythrocytic phase of the *Plasmodium* life cycle where the parasites show tremendous increase in metabolic activities and make use of host cell constituents for their biosynthetic needs.[186] Hemoglobin catabolism, which occurs within the digestive food vacuoles, is one of the important pathways by which these parasites acquire amino acids. The involvement of three classes of enzymes, namely plasmepsins, falcipains, and falcilysin, has been implicated in this process, and each has gained attention as important

chemotherapeutic targets (see below). As the redox-active heme moieties generated during hemoglobin degradation are toxic, the parasites biomineralize them to nontoxic hemozoin (malaria pigment). The ability of chloroquine to inhibit hemozoin formation suggests that this and related compounds may be interfering with the heme-detoxification process, making the parasites susceptible to oxidative stress by heme.[187,188] The exact molecular details of this interference have been the subject of much discussion, and studies over the last several years tend to show that inhibition of hemozoin formation may either be due to the direct complexation of quinolines with hematin (hydroxyferriprotoporphyrin IX), an autooxidation product of heme, or due to a capping effect whereby the drug binds to the growing face of the hemozoin crystal, thus preventing its growth.[189] The ability of members of this class to interfere with heme binding to histidine rich protein II (HRP-II), a protein involved in hemozoin formation,[190] and a recent report showing chloroquine binding with lactate dehydrogenase[191] point toward the possible existence of additional biological targets.

After the emergence of parasites that are resistant to chloroquine, a number of structure–activity relationship (SAR) studies were initiated to understand the stereoelectronic factors that are essential for the observed antiplasmodial action and those characteristics that contribute to parasitic resistance.[186,192] The following general conclusions could be derived from these studies.

1. The weak base property of chloroquine allows it is diffuse through plasma as well as vacuolar membranes. Its protonation under the acidic conditions of the food vacuole traps the molecule inside, leading to accumulation.
2. The 4-amino quinoline nucleus is essential for complexation with hematin; but this alone is not sufficient for the inhibition of hemozoin formation. Simple quinoline or its 3-, 5-, 6-, or 8-amino derivatives do not form noticeable complexes with hematin, whereas its 2- and 4-amino substituted analogs do, and the major component of their stability arises from π–π interactions with the porphyrin system.[193]
3. The aminoalkyl side chain in chloroquine helps in the accumulation of the drug inside the food vacuole and assists in the complexation of the quinoline nucleus with the porphyrin system. Modification of this side chain either by varying its length or attaching new chemical groups can circumvent chloroquine resistance.[186,194] Although this is not a permanent solution to deal with resistance, such modifications have

provided a number of interesting compounds with favorable therapeutic profiles, some of which are presented in Table 3.

Table 3. Various chloroquine analogs having improved activities against resistant strains of the parasite

Compounds	***Biological characteristics***
	Ferroquine (**5**) is ~22 times more potent than chloroquine against resistant strain of *P. falciparum* in vitro. After a 4-day in vivo test in mice infected with *P. berghei* (NS), only 20% showed recrudescence when observed for 60 days, whereas all mice treated with CQ showed recrudescence.[195,196]
	Analogs such as **6**, with shorter side chains (*n*=2–3) or larger chains (*n*=10–12) are almost 10 times more potent than CQ in vitro against resistant strains.[197]
	Compound **7** showed an in vitro IC_{50} value of 49±14 nM (compared to 315±82 nM for CQ) against resistant strains of *P. falciparum*. However, this and related analogs with shorter side chains in general showed low in vivo efficacy and cross resistance with CQ.[198]
	Bis-quinoline (**8**) showed an IC_{50} value of 1.4 nM against W2 clone of *P. falciparum*, (relative to 100 nM for CQ) and 100% cure when tested in vivo against *P. berghei* at 320 mg kg^{-1} dose.[199,200]

4. The presence of chlorine at the 7-position is essential for the inhibition of hemozoin formation and its replacement with other halogens, such as iodine or bromine, do not significantly alter the biological activities of these compounds. Substitution of hydrogens in the quinoline ring with other groups influence the pK_a of the ring as well as the side chain nitrogens and may indirectly affect the stability of the hematin–drug complex.[197,201,202]

An overview of various factors described above is pictorially presented in Figure 3.

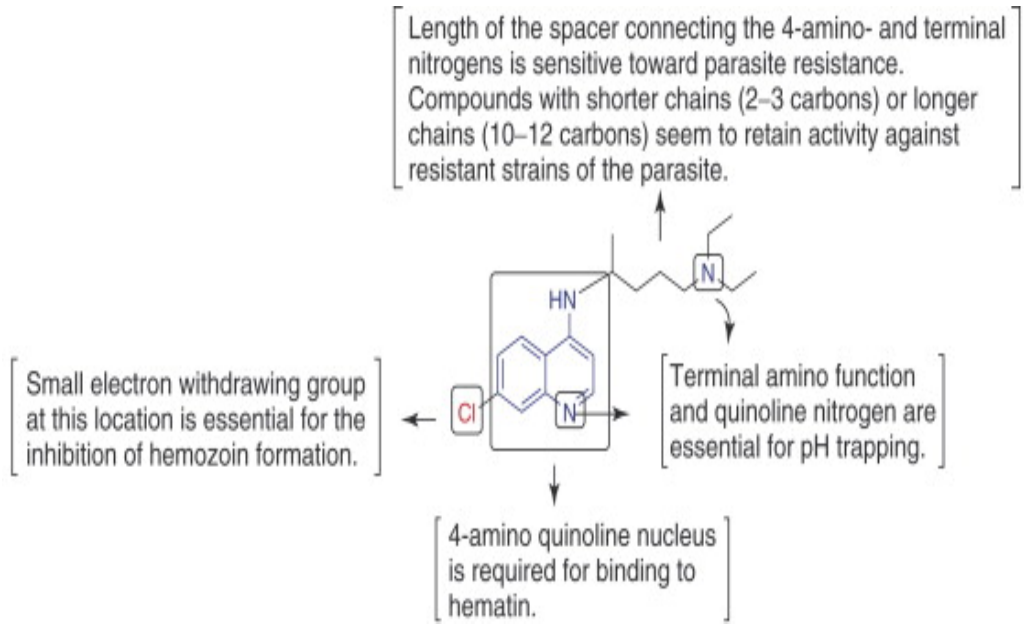
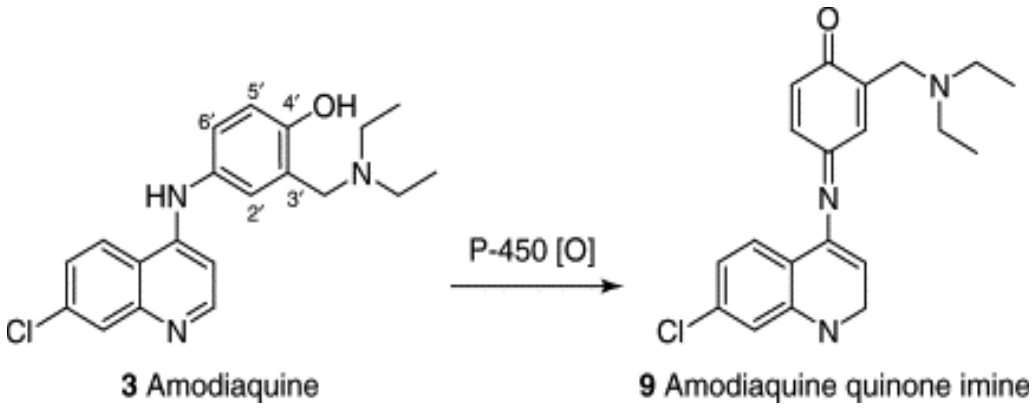


Figure 3. Structural features of chloroquine that contribute to its biological activity.

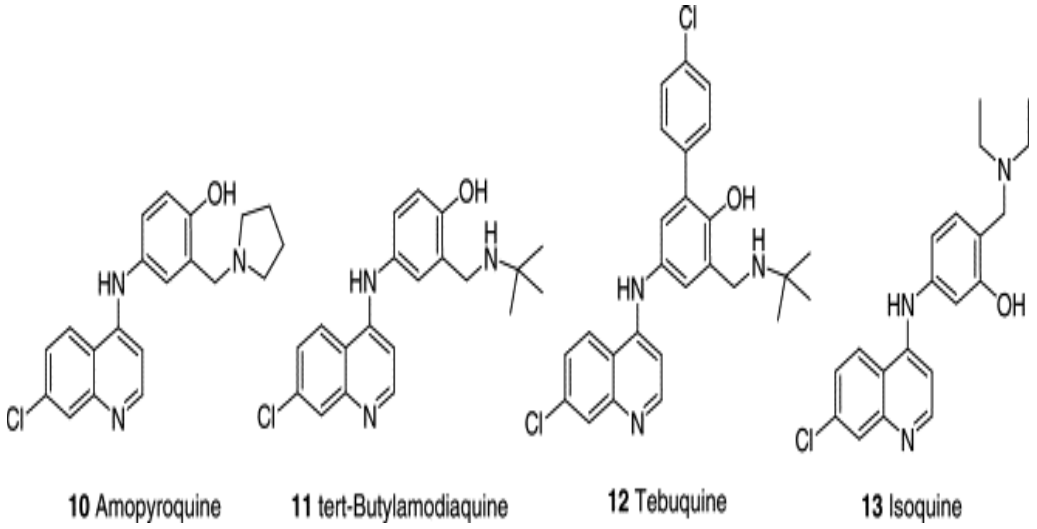
Since toxic side effects limited the use of amodiaquine, there have been several attempts to understand the molecular basis for this toxicity and to develop better candidates devoid of adverse effects. Available evidences indicate that the quinone-imine intermediate **9**, formed as a result of metabolism of AQ in liver, alkylates various biological targets and is responsible for the toxicity.[203]



3 Amodiaquine **9** Amodiaquine quinone imine

Introduction of various groups at the 3' and 5' positions of the amodiaquine side chain was initially considered as a strategy to increase the lipophilicity of drugs and to reduce the cross-resistance which normally arises after side chain metabolism.[204,205] Several compounds in this series have been synthesized and analyzed (e.g., **10**–**12**).[206] Even though these compounds are more potent than AQ in vitro and in vivo, toxicity remains a problem.[207]

In an elegant approach by O'Neill *et al.*, a number of AQ analogs were synthesized by interchanging the position of hydroxy and diethyl-aminomethyl groups and were evaluated for antimalarial potencies and toxicities.[208] It was assumed that the formation of the quinone-imine intermediate is electronically unfeasible in such systems, which, at the same time, possess necessary groups to interact with a biological target. This strategy has given very promising results in initial studies. Thus, compound **13** (isoquine) was found to be more potent than CQ and AQ without any signs of toxicity.



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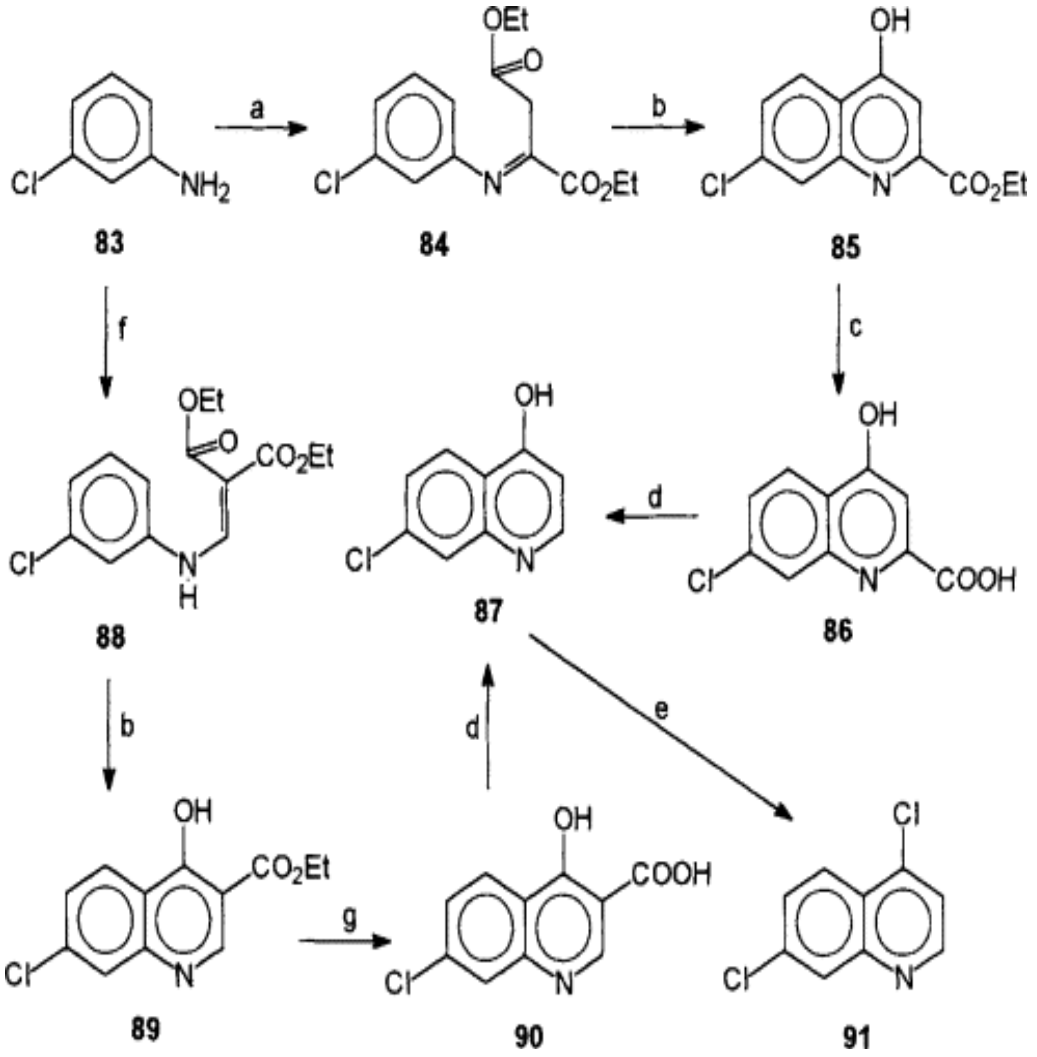
URL: https://www.sciencedirect.com/science/article/pii/B008045044X002273

Approaches to Design and Synthesis of Antiparasitic Drugs

Satyavan Sharma, Nitya Anand, in Pharmacochemistry Library, 1997

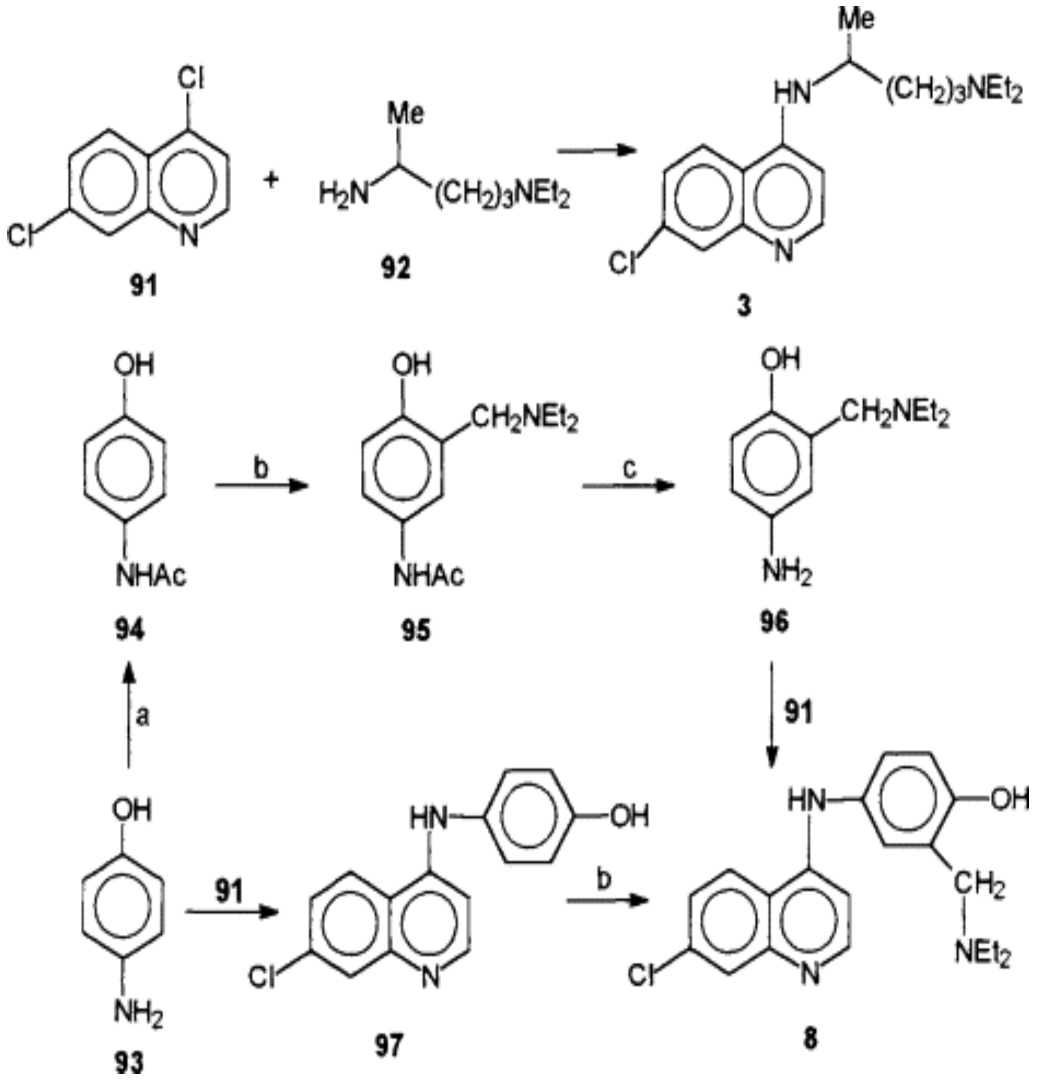
7.1 Chloroquine (3) and amodiaquine

The key intermediate for synthesizing chloroquine, amodiquine and other 4-aminoquinoline drugs is 4,7-dichloroquinoline (**91**), which can be prepared by reacting *m*-chloroaniline (**83**) with diethyl oxaloacetate (EtO-CO-CH_2-CO-COOEt) or ethoxymethylene malonic ester [EtO-CH = $C(COOEt)_2$] as shown in scheme 1 [8,128–133].



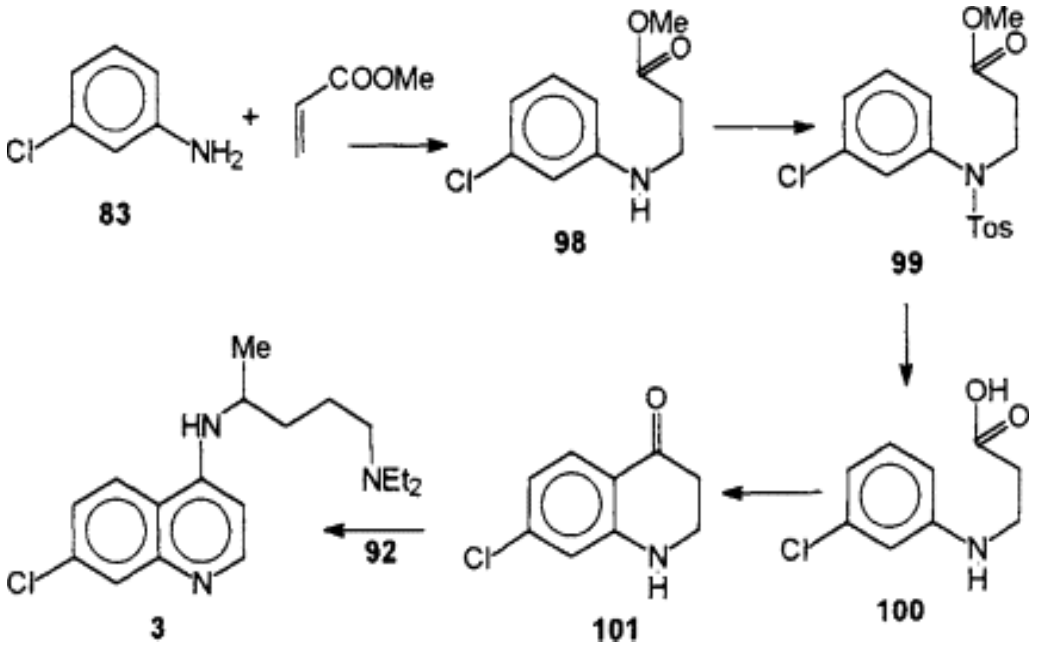
Scheme 1. Reagents: (a) EtOCO-CH_2CO-COOEt, (b) heat and separation of isomers (c) NaOH, heat, (d) heat (250 °C), (e) $POCl_3$, (f) EtOCH = $C(COOEt)_2$, (g) NaOH, heat, HCl

The synthesis of various 4-aminoquinoline antimalarials may be achieved by nucleophilic reaction of **91** with desired amines. Scheme 2 outlines the preparation of chloroquine (**3**) and amodiaquine (**8**) starting from 4,7-dichloroquinoline (**91**) [134–136].



Scheme 2. Reagents: (a) Ac_2O; (b) HCHO, $NHEt_2$ (c) HCl.

Another method to prepare chloroquine (**3**) involves reaction of **83** with methyl acrylate to get via **98** and **99** the adduct **100,** which is converted into 7-chloro-1,2,3,4-tetrahydroquinoline-4-one (**103**). Reaction of **103** with novaldiamine (**92**) under dehydrogenating conditions gives chloroquine in about 25% overall yield [133] (3).



Scheme 3.

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Drugs and Drug Leads Based on Natural Products for Treatment and Prophylaxis of Malaria

Søren Brøgger Christensen, in Evidence-Based Validation of Herbal Medicine, 2015

14.2.2.1.2 Chloroquine

The most successful drug and without comparison, chloroquine [20], was not developed using quinine as a scaffold but methylene blue (Figure 14.6). Ehrlich concluded that the ability of the *Plasmodium* parasite to take up this dye so efficiently had to cause a toxic effect on the parasite. He succeeded in curing two patients with malaria, but the drug was not sufficient efficient for general use [22]. Attempts to optimize the molecule led to chloroquine, the potential of which, however, was first realized after the Second World War [22]. Chloroquine became the drug of first choice in malaria therapy for more than two decades until resistance limited the use of the drug. The resistance is correlated to point mutations in the gene *pfcrt* [26]. The gene codes for a transporter PfCRT. Mutations in the gene like *K76T* has been assumed to remove a positively charged lysine from the transporter thereby enabling it to remove the positively charged chloroquine from the food vacuole [20]. Other

PfCRT mutations, however, also induce resistance, suggesting a more complex situation. Like quinine, chloroquine prevents hemozoin formation [19]. An interesting feature of chloroquine is that the racemic form of this drug is used. The achirality of the hem molecule leads to the expectation that the two isomers have the same affinity toward the biological target, but obviously different distribution or metabolism of the two enantiomers cannot be excluded.

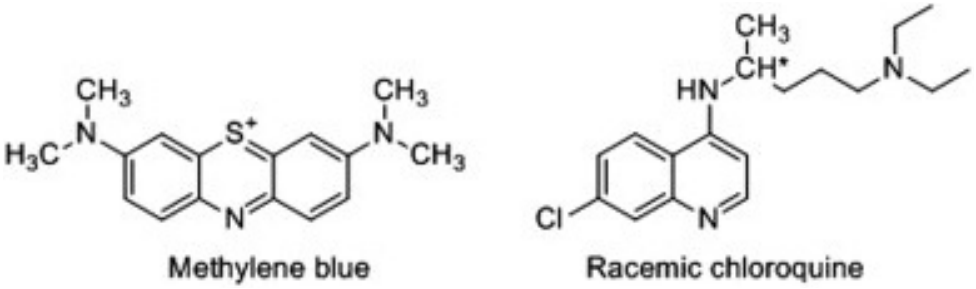

Figure 14.6. Methylene blue and chloroquine. Chloroquine is used as a racemic mixture. The missing chirality of the target molecule (the precipitating hem) must mean that the two enantiomers have the same affinity for the target, but they may be differently metabolized or distributed in the body.

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Antimicrobial Potentiation Approaches: Targets and Inhibitors

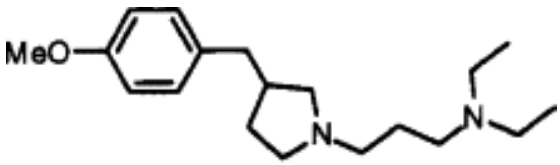
Thomas E. Renau, ... Ving J. Lee, in Annual Reports in Medicinal Chemistry, 1998

Protozoal

The emergence of resistance in the late 1950's to chloroquine, an agent used to treat malaria, severely compromised the effectiveness and use of this drug (3). Studies have demonstrated that chloroquine resistance in *Plasmodium falciparum*, the causative organism, bears close similarities to the MDR phenotype described above and can be reversed by several drugs including verapamil (3). Two genes, *pfmdr1* and *pfmdr2*, have been identified in *P. falciparum* which are approximately 60% homologous to the MDR genes found in mammalian cells (93,94). However, the exact role of these

genes in the emergence of drug resistance remains controversial since there appears to be no correlation between the amplification of the *pfmdr1* gene and resistance to chloroquine, *in vitro* (95).

With growing evidence that chloroquine resistance patterns are modulated *via* a P-gp-like transporter, studies to block the MDR phenotype and potentiate the activity of chloroquine have been reported. For example, chlorpheniramine reverses chloroquine resistance in 11 of 14 P. *falciparum* isolates at 625 nM with no potentiation observed against chloroquine-susceptible clones (96). In another study, fangchinoline, a bis-biphenylisoquinoline, potentiated the activity of chloroquine against a chloroquine-resistant *P. falciparum* strain *in vitro* (97). The compound also potentiated the activity of vinblastine in an MDR cell line approximately 90-fold, indicating it may inhibit the P-gp transporter. WR268954 (**10**), a pyrrolidino alkyiamine, decreases the IC_{50} of chloroquine for drug resistant *P. falciparum* 90-fold when compared to chloroquine alone (98). The compound has weak intrinsic antimalarial activity and may act as a competitive inhibitor of the binding of chloroquine to the putative transporter.



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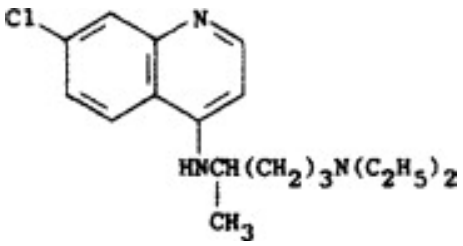
Sun Protection in Man

Homer S. Black, Lesley E. Rhodes, in Comprehensive Series in Photosciences, 2001

30.3.1 Antimalarials

In the past, the 4-amino-quinolines, including chloroquine and hydroxychloroquine, were frequently employed as therapeutic agents for a broad spectrum of light-sensitive disorders. These included systemic lupus erythematous, polymorphic light eruption (PLE), solar urticaria, and porphyria cutanea tarda [34]. Chloroquine, shown here, is a reasonably effective absorber of UV light and has a propensity to accumulate in the epidermis.



Chloroquine

When excreted in sweat after UV exposure, it demonstrates a spectral shift with increased absorption in the 270–310 nm range. An early study reported that chloroquine, when applied topically to human skin, produced a significant decrease in the erythema response, suggesting a strong screening effect [35]. Knox and Freeman [36] demonstrated that orally ingested chloroquine inhibited the recurrence of basal cell carcinomas in a double-blind study of over 200 tumour-prone patients (treated for previous basal cell carcinomas). However, this protective effect did not extend to squamous cell carcinomas and statistical significance washed out after 17 months of the three-year follow-up period. Moreover, Cahn et al. [37] showed that systemically administered chloroquine phosphate did not alter the MED response in patients suffering from PLE. Nor were they able to demonstrate differences in UV absorption of epidermis obtained from patients systemically administered control vehicle or chloroquine. Neither could they detect levels of the drug in the epidermis sufficient to act as a physical sunscreen. They concluded that chloroquine photoprotection could not be due to a light-filtering mechanism [38]. Thus, while the mode of photoprotective action of the antimalarials remains in question, the occasional severe [39] and irreversible side-effects (notably retinopathy) preclude these agents as general photoprotectants [40].

Bionanofibers in drug delivery*

Xin Zhao, ... Wenguo Cui, in Nanobiomaterials in Drug Delivery, 2016

12.2.3.2 Hydrophilic drugs

Hydrophilic drugs, such as the chemotherapeutic drug DOX and antimalarial chloroquine (CQ), can be dissolved in hydrophilic polymers such as gelatin, PEG, PVA, using common solvents such as mixing solution of water and

HFIP for electrospinning. Hydrophilic drugs released from hydrophilic polymer usually exhibit a large initial burst release and a short release period. To circumvent this problem, hydrophobic polymers can be used as an alternative drug carrier; this, however, precludes the use of a common solvent for both polymer and drug. In this case, hydrophilic drugs can first be loaded into drug vehicles, such as MSNs, which are then dispersed in the polymer solution before blending electrospinning (Qiu et al., 2013; Zhao et al., 2015a,c). For instance, Qiu et al. fabricated PLLA–MSN–DOX composite nanofibers, which were found to have a high drug-loading capacity (Qiu et al., 2013) (Figure 12.7). Moreover, the rate and duration of drug release could be tuned by modifying drug and/or MSN concentrations. They demonstrated that the inclusion of DOX-loaded MSNs within the nanofibers resulted in a higher antitumor effect *in vitro*, likely due to a prolonged release and action of the drug.

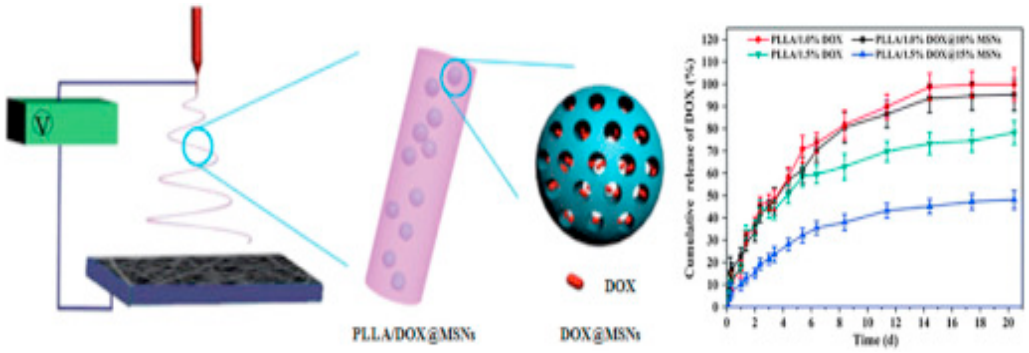


Figure 12.7. Fabrication of PLLA/DOX@MSNs electrospun composite nanofibers and its drug release profile.

Modified from Qiu et al. (2013).

In order to challenge the inability to dissolve drug and polymer in a common solvent, an alternative approach involves dissolution in two immiscible solvents before the mixture is subject to either coaxial or emulsion electrospinning. For example, Zhou et al. loaded antimalarial CQ into HA sol nanoparticles, which were then encapsulated in PLLA nanofibers by microsol/emulsion electrospinning. In this strategy, HA sol nanoparticles successfully preserved the bioactivity of CQ by minimizing its contact with the organic solvent. Also, nanofibers with core–shell morphology were obtained as the soft HA sol nanoparticles were stretched. An *in vitro* release study demonstrated a drug release period of longer than 40 days. It was further observed that the release rate was positively correlated to the concentrations of HA sol nanoparticles and CQ drug (Zhou et al., 2014).

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Medicinal properties of marine plants

Ranjeet Kumar, Ashish Kumar Tewari, in Synthesis of Medicinal Agents from Plants, 2018

11.4.3 Pharmacological Activity of Aplidiopsamine A

Aplidiopsamine A **11.48** was tested for its ability to inhibit the growth of chloroquine sensitive (3D7) and resistant (Dd2) strains of the malarial parasite, *Plasmodium falciparum*. Human cell toxicity was assessed using the normal cell line HEK-293. Aplidiopsamine A was equally active against the two malarial parasite strains (IC_{50} = 1.47 (3D7) and 1.65 μM (Dd2)), and only showed growth inhibition against HEK-293 cells at higher doses, only reaching ~100% inhibition at the highest dose tested (120 μM). Aplidiopsamine A, therefore, represents a novel lead structure that could be further developed into a drug to treat drug-resistant malarial infections (Carroll et al., 2010).

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Antimalarial Agents

Eric Scholar, in xPharm: The Comprehensive Pharmacology Reference, 2007

Targets-Pharmacodynamics

Antimalarial drugs have a variety of targets and mechanisms of action. Many, like chloroquine, amodiaquine, mefloquine, and quinine act on heme in the parasitic food vacuole. In this way, they prevent the polymerization of hemoglobin, which can be toxic to the plasmodium parasite. Others are folate antagonists. Some of the drugs in this class, like pyrimethamine and proguanil, are selective inhibitors of parasitic dihydrofolate reductase, whereas the sulfonamides and sulfones are PABA antagonists and inhibit dihydropteroate synthetase. A third group of antimalarials, such as artemether, produces free radicals that destroy the malaria parasite or inhibit parasitic electron transport. Primaquine may also generate reactive oxygen species that may interfere with electron transport in the parasite. Finally,

there are antibiotics, such as doxycycline, that selectively inhibit protein synthesis in the parasite Tracy and Webster (2001), Scholar and Pratt (2000), Olliaro (2001), Foley and Tilley (1998). The specific target varies with the antimalarial agent. The major of these drugs are most effective against the erythrocytic form of the parasite, although primaquine acts against the hepatic stages and latent tissue forms. For the blood schizoniticides, heme is a frequent target, as is folic acid synthesis, and mitochondrial electron transport.

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Nanobiomaterials Architectured for Improved Delivery of Antimalaria Drugs

B.A. Aderibigbe, H.E. Mukaya, in Nanoarchitectonics for Smart Delivery and Drug Targeting, 2016

Abstract

The increasing occurrence of malaria parasites' resistance to the presently used antimalarial drugs, such as chloroquine, is hindering the fight against malaria. Factors contributing to the drug resistance of antimalarial drugs are: incorrect dosage, patients' noncompliance due to inconvenient dosage schedules, poor drug quality, drug interactions, poor or erratic absorption, reduced uptake of the drug into the parasite, and an increased efflux of the drug out of the parasite. Applications of biomaterials for the design and preparation of drug-delivery systems have been found to improve the therapeutic effects of antimalarial drugs such as: reducing drug resistance, reducing drug toxicity, and a controlled drug-release mechanism. In this chapter, we evaluate the therapeutic efficacy of the presently developed nanobiomaterial-based delivery systems used for antimalarial drugs.

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